Adropin Levels in Polycystic Ovary Syndrome Patients

Polikistik Over Sendromlu Hastalarda Adropin Düzeyi

Adropin in Polycystic Ovary Syndrome

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Özet

Amaç: Polikistik Over Sendromu (PCOS), üreme çağındaki kadınlarda en sık görülen endokrinopatilerden biridir. PCOS olan kadınlar kardiyovasküler hastalık için, hipertansiyon, dislipidemi, diyabet ve obezite gibi klasik risk faktörlerinin yanı sıra C-reaktif protein (CRP), homosistein ve tümör nekroz faktörü-α klasik olmayan risk faktörlerinin de bir artış olduğunu belirtmişlerdir. Adropin enerji hemostazının sürdürülmesinde ve insülin cevabında rolü olduğu düşünülen bir proteindir. Bizim çalışmamızın amacı; insülin direnci ve artmış diyabet riski taşıyan PCOS hasta topluluğunda adropin düzeyinin insulin direnci ile ilişkisini araştırmaktır. Gereç ve Yöntem: Elli yedi hasta (30 adet PCOS hastası ve 27 sağlıklı kontrol) çalışmaya dahil edildi. Her hastanın vücut kitle indeksi ve insulin direnci hesaplandı. Adropin düzeyleri EIA (enzyme immunoassay) metodu kullanılarak ölçüldü. Bulgular: Adropin düzeyi hasta grubunda 10,79 ng/L iken kontrol grubunda 13,02 ng/L olarak bulundu ve aradaki fark istatistiksel olarak anlamlı bulundu (p=0,04). Adropin düzeyi ile insülin, aspartat aminotransferaz (AST), trigliserid (TG) ve insülin direncini yansıtan HOMA değeri (HOMA-IR) düzeyleri arasında anlamlı olarak ters korelasyon saptandı (sırasıyla p=0,03; p=0,03; p=0,04; p=0,02). Tartışma: Çalışmamızda insülin direnci ile ilişkili olan adropin düzeylerinin, PCOS lu hastalarda azalmış olduğu saptanmıştır. PCOS lu hastalarda insülin direnci ile giden klinik durumların değerlendirilmesinde adropin düzeyleri üzerine yeni çalışmalar yapılmasının değerli olacağını düşünmekteyiz.

Anahtar Kelimeler

Polikistik Over Sendromu; Adropin; İnsülin Direnci

Abstract

Aim: Polycystic ovary syndrome (PCOS) is one of the most commonly observed endocrinopathies in women of reproductive age. Women with PCOS are said to have increased classic risk factors for cardiovascular disease, hypertension, dyslipidemia, diabetes, and obesity, in addition to non-classic risk factors such as an increase in C-reactive protein (CRP), homocysteine, and tumor necrosis factor-α. Adropin is a protein thought to play a role in maintaining energy homeostasis and insulin response. The aim of our study is to investigate the relationship between levels of adropin and insulin resistance in PCOS patients with insulin resistance and an increased risk of diabetes.Material and Method: Fifty-seven female patients (30 patients with PCOS and 27 healthy control subjects) were enrolled in this study. All patient's body mass index and insulin resistance were calculated. The adropin levels were measured using commercial kits based on a competitive plasma EIA (enzyme immunoassay) method. Results: The adropin levels in the patient group were 10.79 ng/L, while the value was 13.02 ng/L in the control group, and the difference was statistically significant (p=0.04). There was a significant negative correlation between the adropin levels and the insulin, aspartate aminotransferase (AST), triglyseride (TG), and homeostasis model assessment of insulin resistance (HOMA-IR) levels (p=0.03, p=0.03, p=0.04, and p=0.02, respectively). Discussion: In our study, the adropin level which is associated with insulin resistance, was found to be decreased in patients with PCOS. We think that it would be valuable to conduct new studies for the evaluation of adropin related clinical conditions leading to insulin resistance in patients with PCOS.

Keywords

Polycystic Ovary Syndrome; Adropin Level; Insulin Resistance

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most commonly observed endocrinopathies in women of reproductive age, with a 4–10% prevalence of the form being defined by the National Institute for Child Health and Development (NICHD) [1-4]. Many studies have been published on the long- and short-term effects of PCOS on women's health, with late complications such as increased cardiovascular, metabolic, and oncologic risks, in addition to an increased incidence of early complications like decreased fertility and obstetric results, being reported [5]. Due to PCOS's heterogeneous nature, uncertain pathogenetic mechanisms, and complicating factors such as obesity, it is difficult to clearly define the scale of these complications [5]. As previously reported [6-8], women with PCOS are said to have increased classic risk factors for cardiovascular disease, hypertension, dyslipidemia, diabetes, and obesity, in addition to non-classic risk factors such as an increase in C-reactive protein (CRP), homocysteine, and tumor necrosis factor-α [9].

In addition to affecting significant metabolic processes such as reproduction, PCOS is an important risk factor for type 2 diabetes. Women with PCOS have been observed to have insulin resistance independent of obesity [10]. Indeed, insulin resistance (IR) is observed in 30% of lean women with PCOS and in 95% of obese women with PCOS [11,12].

Adropin was first discovered in 2008 by Kumar et al. and it is a protein thought to play a role in maintaining energy homeostasis and insulin response [13]. It is coded by the gene (Enho) related to energy homeostasis, which is expressed in the liver and brain. Further, adropin appears to be effective in heart disease, insulin resistance, disrupted glucose tolerance, and diabetes [14-16].

The aim of our study is to assess the adropin parameter in that segment of the PCOS population with insulin resistance and an increased risk of diabetes.

Material and Method

Fifty-seven female patients (30 patients with PCOS and 27 healthy control subjects) were enrolled in this study. Each participant signed an informed consent form in accordance with the requirements of the Declaration of Helsinki. The study was approved by the local ethics committee of Canakkale Onsekiz Mart University.

We included patients who were newly diagnosed with PCOS in our study. The diagnosis of PCOS was based on the 2003 Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group's diagnostic criteria: oligo or anovulation, clinical and/or biochemical hyperandrogenism, or positive ultrasound presentation of polycystic ovaries determined by transvaginal scan and/or abdominal scan and defined as the presence of 12 or more follicles measuring 2–9 mm in diameter in each ovary and/or an ovarian volume of >10 mL [6]. Our exclusion criteria were: a history of cardiovascular disease, cancer, systemic infection, diabetes mellitus (DM), liver disease, renal disease, hematological disease, thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinemia, those who had received medical treatment, and those who smoked or used alcohol. The control group was composed of healthy female volunteers. Demographic, anthropometric, and clinical variables were also recorded.

The body mass index (BMI) of each patient was calculated using the Quetelet index and then dividing the weight by the square of the height (weight / height ^{2}- kg / m^2). Insulin resistance was calculated using the Homeostasis Model of Assessment-Insulin Resistance index (HOMA-IR) formula: fasting blood glucose (FBG; mmol/L) × fasting insulin (mU/L) / 22.5.

Venous blood samples (5 mL) were drawn simultaneously from participants between 09:00 AM and 10:00 AM during 3–5 days of the follicular phase. All patients and controls fasted for one night prior to sample collection. The blood samples were drawn into vacutainer EDTA aprotinin tubes for adropin and then stored at -80°C until the time of analysis. The samples taken into tubes with K3EDTA/Aprotinin were immediately centrifuged at 4000 rpm for 10 minutes. The plasma was separated from the whole blood samples for adropin measurement and then stored at -80°C until the study day. There was no repeated freeze-thaw. The adropin (Cat No. EK-032-35, Phoenix Pharmaceuticals, Burlingame, CA, USA) levels were measured using commercial kits based on a competitive plasma EIA (enzyme immunoassay) method. All measurements were performed twice. The results were determined using an ELISA reader (model ELX 808 I). For the adropin, the intra-day and inter-day % CV (coefficient of variation) values were <10% and <12, respectively.

Statistical Analysis

SPSS version 19.0 (IBM, Chicago, IL, USA) was used for all statistical analyses, and a p value of <0.05 was considered statistically significant. Continuous variables were expressed as mean ± standard deviation. The t-test and the Mann-Whitney U test were used for the parametric and non-parametric variables, respectively. The correlation between the parameters was analyzed using the Pearson and Spearman methods for the parametric and non-parametric variables, respectively.

Results

The study included a total of 57 participants (30 PCOS patients and 27 healthy controls). The mean age of the patient group was 21.56 years, while it was 21.66 in the control group (p=0.105), although the difference was not statistically significant. The mean body mass index of the patient group was 26.86, while it was 21.39 for the control group, with the difference being statistically significant (p<0.001). The HOMA-IR values of the patient group were found to be higher than those of the control group, and the difference was statistically significant (3.59 and 2.15, respectively; p=0.004). The demographic characteristics and biochemical values of the PCOS patients and the healthy controls are shown in Table 1.

The adropin levels in the patient group were 10.79 ng/L, while the value was 13.02 ng/L in the control group, and the difference was statistically significant (p=0.04) (Figure 1). There was a significant negative correlation between the adropin levels and the insulin, AST, TG, and HOMA-IR levels (p=0.03, p=0.03, p=0.04, and p=0.02, respectively). The correlation values between adropin and the other parameters are given in Table 2.

Discussion

In our study, we found that the adropin levels of the PCOS patients were lower when compared to those of healthy individu-

als. We identified an inverse correlation between adropin and metabolic disorders in PCOS patients, especially insulin resistance.

The disorders observed in polycystic ovary syndrome patients are not linked to a single cause. A variety of genetic disorders combined with environmental conditions cause PCOS. Insulin resistance appears to play a central role in the condition, and it is found in 50–70% of cases independent of obesity [17, 18]. Insulin resistance and the associated development of excess insulin release increase the production of androgen [19]. Excess androgen in turn causes menstrual disorders, development of ovarian cysts, and hirsutism [1]. Insulin resistance also increases the risk of developing glucose intolerance, type 2 DM, hypertension, dyslipidemia, and cardiovascular disorders [19]. Hyperinsulinemia and hyperandrogenemia are the two main factors in PCOS development; however, why they develop and their correlation to each other have not yet been fully explained [17, 20]. Lowering patients' insulin levels pharmacologically prevents hyperinsulinemia, lowers androgen levels, and improves ovarian function [17, 20]. However, lowering patients' androgen levels does not appear to have an impact on insulin resistance and hyperinsulinemia. These findings suggest that while hyperandrogenemia does not cause insulin resistance, insulin resistance causes hyperandrogenemia. When examined from this viewpoint, the presence of insulin resistance in PCOS patients plays an important role in the pathogenesis of the condition. While insulin resistance is observed in 30% of lean PCOS patients [11], it is observed in 95% of obese PCOS patients [12]. In our study, we found that the insulin resistance in the PCOS group was higher than that in the control group.

Table 1. Demographical characteristics and biochemical values of controls and PCOS patients.

	PCOS Group (N:30)	Control Group (N:27)	P Value
Age(years)	21,56±0,79	21,66±0,31	0,105
BMI(kg/m2)	26,86±1,31	21,39±0,53	0,000
Glucose(mg/dl)	92,82±1,55	88,62±1,18	0,03
Insulin(mU/L)	15,56±1,7	9,75±1,15	0,007
AST (U/L)	17,87±1,5	14,55±0,51	0,01
ALT (U/L)	18,2±4,01	12,51±0,75	0,44
LDL(mg/dl)	108,6±7,24	90,84±5,83	0,06
HDL(mg/dl)	58±3,9	70,24±3,72	0,02
TG(mg/dl)	98,68±11,89	61,77±4,04	0,02
TSH (uIU/ml)	2,4±0,21	1,9±0,17	0,08
HOMA-IR	3,59±0,38	2,15±0,25	0,004
Adropin(ng/L)	10,79±0,82	13,02±0,71	0,04

Abbreviations: BMI; body mass index, LDL; low density lipoprotein, TG; triglycerides, HDL; High density lipoprotein, AST; aspartate aminotransferase, ALT; Alanine aminotransferase, TSH; thyroid stimulating hormone, HOMA-IR; Homeostatic Model Assessment-Insulin Resitance

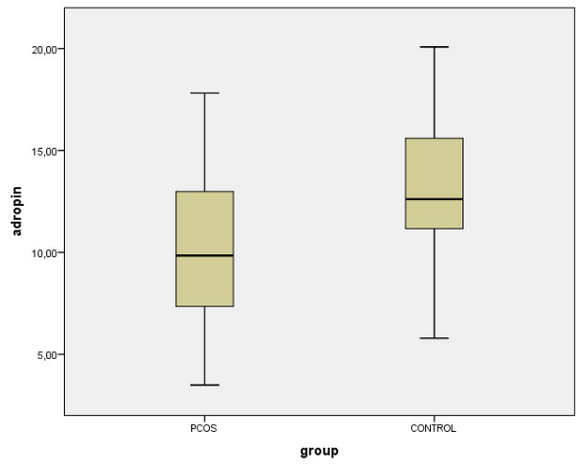

Figure 1. Levels of Adropin

Table 2. Correlation analysis between Adropin and other parameters in the whole study groups.

	r	p
Age	0,14	0,27
BMI	-0,18	0,19
Glucose	-0,07	0,57
Insulin	-0,3	0,03
AST	-0,3	0,03
TSH	-0,92	0,5
LDL	-0,15	0,27
HDL	0,16	0,27
TG	-0,28	0,04
HOMA-IR	-0,3	0,02

Celik et al. [16] showed that the adropin levels were lower in the blood and cord serum of mothers with gestational diabetes when compared to the control group. Further, Kumar et al. showed that there was an association between adropin deficiency, increased adiposity, and insulin resistance [13]. Increased adropin levels in the circulation occur as a response to metabolic stress, and such increased levels have been shown to reduce insulin resistance and glucose intolerance [13]. Wu et al. determined that the adropin levels were significantly reduced in type 2 DM patients when compared to non-diabetics [21]. All of these results show that adropin may be a protective factor against hepatosteatosis and hyperinsulinemia regulating glucose and lipid metabolism [22]. In our study, the aspartate aminotransferase (AST) and insulin resistance levels were found to be higher in the PCOS group when compared to the control group.

A study by Akçlar et al. found that the adropin levels in streoptozotocin-induced type 2 diabetic rats were lower when compared to those of the control group. The researchers later found that after intraperitoneal adropin administration, there was a significant reduction in the starvation plasma glucose, HOMA-IR, and HbA1c (%) levels, while the serum insulin and adropin levels increased. The same study showed that following adropin administration, as the high density lipoprotein (HDL) levels increased, the triglyceride levels decreased and so adropin had significant effects on lipid metabolism. In our study, we found a significant inverse correlation between the HOMA-IR and triglyceride levels and adropin. The results of all these studies show that adropin may have a beneficial impact on the prevention of diabetic complications linked to disrupted glucose metabolism.

Studies of diabetic rats have shown previously increased hepatic enzymes such as AST, ALT, ALP, and GGT to be reduced after adropin administration, and they have stated that adropin had a hepatoprotective effect [22, 23]. In our study, we found that the AST levels were significantly high in the PCOS group,

and we showed that there was a significant inverse correlation between the adropin levels and the AST levels.

In our study, the adropin level which is associated with insulin resistance, was found to be decreased in patients with PCOS. We think that it would be valuable to conduct new studies for the evaluation of adropin related clinical conditions leading to insulin resistance in patients with PCOS.

Competing interests

The authors declare that they have no competing interests.

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